ment of the AMV. If an upper limit of normal of 0.5 cm^2 is set for the total area subtended by both leaflets in both views, this criterion is 100% sensitive and 82% specific for the diagnosis of MVP. *Conclusions:* Though TEE demonstrates greater systolic mitral leaflet displacement in MVP than in NORMAL, there is overlap in the range of superior systolic displacement of the mitral valve into the left atrium between MVP pts and NORMAL subjects. The presence of mild superior systolic displacement of the leaflets relative to the annular hinge points by TEE is inadequate to unambiguously identify MVP pts.

987-106 Accuracy of Aortic Valve Area Measurement by Multiplane Transesophageal Echocardiography in Aortic Stenosis

Yvette F. Bernard, Nicolas F. Meneveau, Thierry J. Anguenot, Jian Zhang, François Schiele, Alain Vuillemenot, Jean-Pierre Bassand. *University Hospital Saint-Jacques, Besançon, France*

To determine whether planimetry of the aortic valve opening using multiplane transesophageal echocardiography (TEE) is accurate, 46 consecutive patients (pts) suffering from calcific aortic stenosis (AS) were enrolled in a prospective study. All the pts, 26 M, 20 F, aged 67 ± 11 yrs (43 to 81) had a transthoracic (TTE) and a multiplane TEE using a 5 MHz annular mechanical probe (Vingmed, Norway), within 24 hours before catheterization (cath.). At TTE, aortic valve area (AVA) was calculated by the continuity equation (CE). At TEE, AVA was measured by planimetry of the orifice in a short axis view, obtained with a 40 to 70° rotation of the imaging plane from the initial plane, with thorough searching of the smallest orifice as possible in early systole. Numerical images, recorded on optical disks, were analyzed by 2 independent observers unaware of the results of cath. Right and left heart cath. with measurement of simultaneous left ventricle (LV) to aorta gradients (gr) was performed in all pts and AVA was calculated using the Gorlin formula. Valve area measured at TEE and with the CE correlated well with AVA measured at cath.: $r = 0.92$ for TEE, $p < 0.001$ and $r = 0.83$ for CE, $p < 0.01$.

	TEE (1)	TTE (2)	Cath (3)
AVA (cm^2)	0.63 ± 0.25	0.62 ± 0.20	0.63 ± 0.20
Max gr (mmHg)	/	89 ± 29	87 ± 27
Mean gr (mmHg)	/	58 ± 22	54 ± 21

$p < 0.001$ for (1) vs (3), $p < 0.01$ for (2) vs (3), $p < 0.01$ for (1) vs (2), for AVA

Conclusion: Planimetry of the aortic valve using multiplane TEE is accurate to measure AVA in AS and might be proposed as an alternative to hemodynamic study in pts with low gradients and poor LV function.

987-107 Transesophageal Doppler Analysis of Coronary Sinus Flow: A New Method to Assess the Severity of Tricuspid Regurgitation

José Zamorano, Carlos Almería, Fernando Alfonso, Luis Alonso, Vicente Peral, Luis Sánchez-Harguindey. *Hospital Universitario, Madrid, Spain*

Our aim was to assess the differences in the Doppler flow pattern of the coronary sinus (CS) in patients without tricuspid regurgitation (TR) and with mild (Mi), moderate (Mo) or severe (Se) TR. For this purpose, 35 patients without TR and 70 patients (mean age 57 ± 8 years, 57% males) with different degrees of TR (27 Mi, 14 Mo, 29 Se) underwent a prospective study in which the Doppler flow pattern of the CS obtained by transesophageal echocardiography was analyzed. Adequate Doppler signals of the CS were obtained in 22 (63%) patients without TR and in 50 (71%) patients with TR (18 Mi [65%], 10 Mo [73%], 22 Se [75%]). The CS flow was analyzed by TEE in a transverse plane, showing its drainage into the right atrium, close to the tricuspid valve.

All patients without TR or with Mi TR showed a typical CS Doppler flow pattern with 2 waves, a late systolic one and another diastolic with larger amplitude and velocity. When we analyzed those patients with Se TR, the late systolic flow became reversed (retrograde) and a Color-Doppler turbulent flow in the CS was found in 96% of them. This reversed systolic wave (RSyW) was also found in 50% of the patients with Mo TR, all of them with eccentric regurgitation jets. The sensitivity (SE), specificity (SP) and diagnostic accuracy (DA) of the presence of a RSyW in the CS for the diagnosis of severe TR was 95%, 82% and 81% respectively.

In conclusion, significant TR modifies the CS flow pattern assessed by transesophageal echocardiography. The presence of a reversed systolic flow in the CS can be a new sign with good SE, SP and DA in the diagnosis of severe tricuspid regurgitation.

988 Anticoagulation, Antithrombolytic Therapy and Acute Myocardial Infarction

Wednesday, March 22, 1995, 9:00 a.m.–11:00 a.m.
Ernest N. Morial Convention Center, Hall E
Presentation Hour: 10:00 a.m.–11:00 a.m.

988-1 Toward Establishing Anticoagulation Guidelines for Intravenous Heparin Administration Among Patients with Myocardial Infarction Given Tissue Plasminogen Activator

Richard Becker, Christopher Cannon, Dorinda George, Joseph Loscalzo, TIMI 5 Investigators. *Thrombosis Research Center, University of Massachusetts Medical School, Worcester, MA*

Heparin is recommended in patients with acute myocardial infarction (MI) treated with tPA to prevent early coronary arterial reocclusion. Although prior clinical studies suggest that an aPTT of at least 1.5 times control is required, experimental evidence has supported more aggressive degrees of anticoagulation (≥3 times control). To date, the benefit and potential risks of aggressive heparin strategies have not been explored fully. In TIMI 5, 246 patients with acute MI received accelerated tPA, oral aspirin and 5 days of either intravenous heparin (n = 79) or r-desulfatohirudin (n = 157). Cardiac catheterization was performed at 90 minutes and again at 18 to 36 hours.

Coronary Angiography (18 to 36 hours)

	6 hour aPTT		12 hour aPTT		6, 12 hour aPTT	
	TIMI 3	TIMI 0,1,2	TIMI 3	TIMI 0,1,2	TIMI 3	TIMI 0,1,2
90 Min Angio						
TIMI 2,3	74.6	83.9	66.6	77.2	72.9	93.5
TIMI 0,1	–	107.5	–	70.2	–	90.3

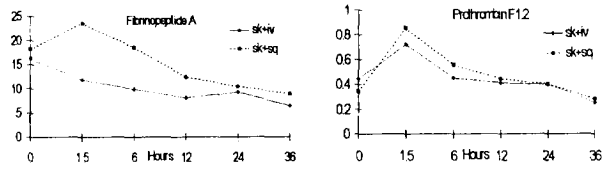
All aPTT's represent median values; no comparison was statistically significant

Major hemorrhage (based on standard TIMI criteria) occurred in 23.3% of heparin-treated patients. A 12-hour aPTT greater than 75 seconds was observed in 92% of patients experiencing major hemorrhagic complications. We conclude that aggressive heparin strategies striving for an aPTT beyond 2.5 times control do *not* offer additional benefit but are associated with an increased risk of major hemorrhage.

988-2 Thrombin Activity, but not Generation, is Inhibited by Intravenous Heparin Following Thrombolysis: Results from the GUSTO Hemostasis Substudy

Brian S. Crenshaw, Richard C. Becker, Christopher B. Granger, Russell P. Tracy, Costas T. Lambrew, Allan M. Ross, Robert M. Califf, Eric J. Topol, Edwin G. Bovill, GUSTO Investigators. *Duke Medical Center, Durham, NC*

Although thrombolytic therapy has been shown to improve survival in the setting of acute myocardial infarction, failure to reperfuse and reocclusion, both felt to be mediated in part by thrombin, continue to be significant problems. To study the impact of heparin on thrombin in thrombolytic treated patients, we evaluated hematologic parameters after administering streptokinase (SK) in GUSTO patients receiving either immediate IV heparin or delayed SQ heparin. Thrombin generation was estimated by assay for prothrombin fragment 1.2 (F1.2) and thrombin activity by fibrinopeptide A (FpA). 67 patients randomized to SK and IV heparin and 63 patients randomized to SK and SQ heparin were included. IV heparin was given as a 5000 U bolus followed by 1000–1200 units per hour adjusted to an aPTT of 60–85 seconds, and SQ heparin was given as 12,500 U twice daily beginning 4 hours after thrombolytic therapy.



FpA (ng/ml) and F1.2 (ng/ml) levels increased after starting thrombolytic therapy among patients treated with SQ heparin, in whom steady-state heparin levels do not occur for at least 24 hours. The FpA increase was inhibited with IV heparin. On the other hand, IV heparin did not inhibit the rise in F1.2 or significantly suppress it below baseline over the course of therapy.

Conclusion: In the first 24 hours following thrombolytic therapy, IV heparin suppresses the increase in thrombin activity but not the increase in thrombin generation. Strategies to inhibit factors earlier in the cascade (i.e., Factors V,

IX, and X), by suppressing thrombin generation, may be an important goal for future management of acute coronary syndromes.

988-3 Is there a Circadian Variation in Anticoagulation Response to Hirudin Following Acute Myocardial Infarction?

Timothy D. Henry, Richard C. Becker, Christopher P. Cannon, Carolyn H. McCabe, Joseph Loscalzo, TIMI 5 Investigators. *Hennepin County Medical Center, Minneapolis, MN*

There is a well-described circadian variation in the occurrence of acute thrombotic coronary syndromes. Likewise, a circadian variation in anticoagulant response to heparin has been reported with a peak effect between 00:00 and 04:00 and a nadir 08:00 to 12:00 hours. This contributes to variability in aPTT's and may be clinically important, predisposing to increased thrombotic events in the morning and bleeding events at night. The reason for this variation is unclear. TIMI-5 was a pilot trial of hirudin, a specific direct thrombin inhibitor, with t-PA and aspirin in acute myocardial infarction. To determine if a circadian variation in anticoagulant response to hirudin is present, we examined aPTT results obtained using Ciba-Corning 512 monitor every 12 hours during the 5-day constant infusion in 87 patients at 3 different fixed infusion rates (0.05, 0.10, 0.20 mg/kg/hr). Data for aPTTs drawn during 4 time periods are expressed in seconds: mean ± SD (# of aPTTs).

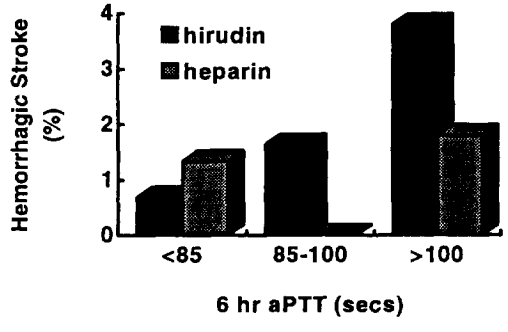
Dose	00:00–06:00	06:00–12:00	12:00–18:00	18:00–24:00
0.05	63 ± −14 (64)	67 ± −18 (69)	62 ± −16 (69)	66 ± −16 (58)
0.10	81 ± −21 (60)	75 ± −21 (70)	74 ± −19 (59)	72 ± −21 (71)
0.20	83 ± −12 (16)	94 ± −23 (4)	79 ± −16 (18)	73 ± 12 (4)
Total	73 ± −19 (140)	72 ± −21 (143)	69 ± −19 (146)	69 ± −19 (133)

There were no significant differences in aPTT results within dosing groups or the total patient population for the designated time periods. *Conclusion:* Unlike heparin, there does *not* appear to be a circadian variation in anticoagulant response to hirudin in patients with acute myocardial infarction. This may contribute to the improved stability in aPTTs observed with hirudin and has potential clinical importance for both bleeding and thrombotic events.

988-4 Hemorrhagic Stroke Associated with High aPTTs Following Thrombolytic Therapy and Heparin or Hirudin

Cristopher Granger, Frans Van de Werf, Mark Horrigan, Robert Califf, Lynn Woodlief, Eric Topol, GUSTO IIa Investigators. *Duke University Medical Center, Durham, NC*

In GUSTO IIa, 2564 patients with acute coronary syndrome with ST deviation and symptoms within 12 hours were randomized to hirudin (0.6 mg/kg bolus, 0.6 mg/kg/hr infusion with out adjustment) or IV heparin (5,000 U bolus, 1100 to 1300 U/hr adjusted to a target aPTF of 60–90 seconds) for 3–5 days. The 26 patients who suffered hemorrhagic stroke, as expected from previous studies examining risk factors, were older (median age 71 vs 65), had higher initial systolic blood pressure (142 vs 134 mmHg) and were more commonly female (42 vs 31%). Unexpectedly, hemorrhagic stroke patients weighed more (82 vs 77 kg), which may have reflected weight-adjusted dosing and consequent administration of more anticoagulant. Of the 26 patients, 23 were treated with thrombolytic therapy. In spite of concern over renal dysfunction contributing to increased risk, the baseline and 48 hour creatinine was similar among hirudin treated patients with (1.2,1.2) and without (1.1,1.1) hemorrhagic stroke. APTT was a predictor of hemorrhagic stroke, particularly in the hirudin assigned group:



Multivariable analysis will help to determine the relative importance of risk factors in GUSTO IIa for hemorrhagic stroke, and whether the elevated aPTTs appear to fully explain the increased risk. These data illustrate the narrow therapeutic window for antithrombin therapy in conjuction with thrombolysis.

988-5 Aspirin-induced Reperfusion in Acute Myocardial Infarction

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The beneficial effect of aspirin (ASA) in unstable angina is well established, yet data on effect of ASA during the hyperacute phase of myocardial infarction (AMI) is limited. We evaluated the effect of early chewed ASA administration on reperfusion rate and hospital outcome in 90 consecutive AMI patients treated at home or in the Emergency Room. All patients had ischemic chest pain of ≥30 minutes, associated with ≥2 mm ST↑. Early reperfusion within 30 minutes occurred in 42 patients (46.7%); only 3 patients needed thrombolysis. In 27 controls reperfusion occurred in 7 patients (25.9%); p = 0.05. No difference in hospital outcome was observed between patients with ASA-induced reperfusion and patients treated by thrombolytics.

Conclusion: 1) Chewed ASA taken early in the hyperacute phase of AMI induced sustained reperfusion in a significant number of patients (46.7%); 2) The above results call for on-scene early administration of chewed ASA in all suspected AMI patients.

988-6 Influence of Pre-Hospital Heparinisation on Early Patency Rate of Infarct Related Artery in Acute Myocardial Infarction

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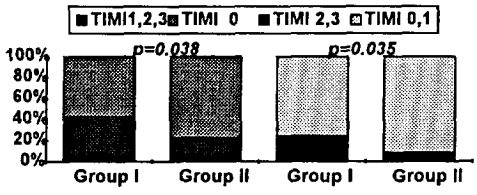
The aim of this study was to assess the influence of pre-hospital treatment with intravenous heparin on the early patency rate of the infarct related artery in acute myocardial infarction. The inclusion criteria were: beginning of chest pain in the 6 hours preceding admission, ST segment elevation ≥1 mm in at least two leads of the standard ECG and no contraindications to antithrombotic treatment. One hundred and twenty four patients with these criteria were divided into 2 groups. Forty five patients (group I) were treated with 5,000 units of heparin i.v. before admission to hospital. Seventy nine patients (group II) did not receive heparin before hospitalisation. All patients in both groups were put on Aspirin 150 mg p.o., nitro-glycerine and analgesics before admission. The mean period from the beginning of the chest pain was 2.7 ± 1.5 hour in group I and 2.8 ± 1.4 hour in group II (p = NS). Both groups did not differ in relation to age, sex, risk factors and previous incidence of myocardial infarction. In the emergency room all patients were put on heparin and nitro-glycerine infusions i.v. and were transferred immediately to the catheterisation laboratory for coronary angiography. The flow through the infarct related artery was assessed according to the TIMI classification. Patent infarct related arteries (i.e. TIMI flow grade 1, 2 or 3) were observed in 19 patients (42.2%) in group I and in 18 (22.8%) in group II (p = 0.038). Successful reperfusion (defined as TIMI grade 2 or 3) was present in 11 patients (24.4%) in group I and in 7 (8.8%) in group II (p = 0.035).



This pilot study suggests that pre-hospital treatment with intravenous heparin can significantly improve flow in infarct related arteries. A prospective randomised study is needed to confirm these results.

988-7 Endothelin $ET_{A/B}$ Receptor Antagonist Reduces Infarct Size: A Novel Therapy for Acute Myocardial Infarction

Joao V. Vitola, John Holsinger, Mervyn B. Forman, Edwin K. Jackson, Masatoshi Kawana, Thomas Quertermous, John J. Murray. *Vanderbilt University, Nashville, TN; University of Pittsburgh, Pittsburgh, PA*

We have previously shown that regional myocardial ischemia followed by reperfusion (rep) significantly enhances cardiac release of the potent vasoconstrictor endothelin (ET). We now examine the association of ET production and myocardial blood flow (MBF) in rabbits (n = 14) undergoing 30 min of circumflex occlusion and 3 hrs of rep. MBF was measured with radioactive microspheres at baseline, 15 min into occlusion, 1 min, 1 and 3 hrs into rep. Utilizing molecular biology techniques, ET_1 mRNA was measured at 3 hrs and found to be elevated in the central ischemic zone (CIZ) compared to the non ischemic zone (NIZ). In a second study we investigated the effects of exogenous ET_1 and PD145065 (an $ET_{A/B}$ receptor antagonist) on infarct size of rabbits undergoing 30 min of circumflex occlusion and 48 hrs of rep.